

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY



(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 22 NOV 2005

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Applicant's or agent's file reference JAF-PB60384	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/EP2004/007668	International filing date (<i>day/month/year</i>) 08.07.2004	Priority date (<i>day/month/year</i>) 11.07.2003
International Patent Classification (IPC) or national classification and IPC A61K9/14		
Applicant GLAXO GROUP LIMITED et al.		
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> <i>sent to the applicant and to the International Bureau</i> a total of 3 sheets, as follows:</p> <p style="margin-left: 40px;"><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>		
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>		
Date of submission of the demand 29.04.2005	Date of completion of this report 22.11.2005	
Name and mailing address of the International preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Muller, S Telephone No. +31 70 340-2080 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/007668

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-20 as originally filed

Claims, Numbers

1-19 received on 09.05.2005 with letter of 29.04.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☒ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:
- see separate sheet**

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 19, with respect to industrial applicability
- because:
- ☒ the said international application, or the said claims Nos. 19, with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):
- see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☒ no international search report has been established for the said claims Nos. 19, with respect to industrial applicability
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
 - ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-19
Inventive step (IS)	Yes: Claims	
	No: Claims	1-19
Industrial applicability (IA)	Yes: Claims	1-18
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item II

Priority

Earlier WO application WO-A-03088943 D1 published on 30 October 2003 claims the priority date of 13 April 2003. It discloses (see page 2, lines 22-28 and example C on page 13) dry powder pharmaceutical compositions suitable for inhalation comprising a pharmaceutical active agent (such as the beta-2-adrenoreceptor agonists of the present application), an excipient (lactose) and a derivatised carbohydrate in particulate form (cellobiose acetate). Particulate derivatised carbohydrates (cellobiose octaacetate) are used in order to improve stability performance, for example, by reducing the deterioration in fine particle fraction following exposure and humidity.

The subject matter of claims 12,13,18 and 19 is therefore explicitly anticipated in D1. It is also stressed that a **newly discovered technical effect** (such as chemical interaction or chemical degradation) does not confer novelty on a claim directed to the use of a known substance for a **known non-medical purpose** (improved stability) if the newly discovered technical effect already underlies the known use of the known substance. Consequently, the subject-matter of claims 1-11,14-17 is implicitly anticipated in D1.

The application GB0316335 (date of filing 11 July 2003) to which the priority claim of the present application is directed, is therefore not the application disclosing for the first time some of the subject-matter of the present EP application. As some of the subject-matter as described above was disclosed in a still earlier application D1 originating from the same applicant (Glaxo Group Limited), the application GB0316335 is in fact not the "first application" in the sense of Article 8 PCT (see also Guidelines C.V.1.4). Therefore, the priority claim is invalid for the subject-matter already disclosed in the still earlier application D1 and document D1 will be considered as forming part of the prior art.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claim 19 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can

also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited Document

The following document D1 is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO 03/088943 A (BULSARA PALLAV ARVIND ; GLAXO GROUP LTD (GB);
ROCHE TREVOR CHARLES (GB) 30 October 2003 (2003-10-30)

2. Novelty

A newly discovered technical effect (such as chemical interaction or chemical degradation) does not confer novelty on a claim directed to the use of a known substance for a **known non-medical purpose** (improved stability) if the newly discovered technical effect already underlies the known use of the known substance.

D1 discloses (see page 2, lines 22-28 and example C on page 13) the use of particulate derivatised carbohydrates (cellobiose octaacetate) in dry powder pharmaceutical compositions for inhalation therapy in order to improve stability performance. Said compositions further comprise a pharmaceutical active agent (like the beta2-adrenoreceptor agonists of the present application) and an excipient (lactose). The subject-matter of claims 1-19 is therefore not new (Article 33(2) PCT).

3. Inventive Step

Claims 1-19 not being new are also not inventive (Article 33(3) PCT).

4. Industrial applicability

Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). Claims 1-18 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

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EPO - DG 1

09 05 2005

CLAIMS

(77)

1. Use of a sugar ester to inhibit or reduce chemical interaction between an active ingredient substance and a carrier in a solid pharmaceutical formulation, wherein the active ingredient substance is susceptible to chemical interaction with the carrier.
2. Use of a sugar ester to inhibit or reduce chemical degradation of an active ingredient substance in a solid pharmaceutical formulation comprising the active ingredient substance and a carrier, wherein said active ingredient substance is susceptible to chemical interaction with said carrier.
3. Use as claimed in claim 1 or claim 2 wherein the sugar ester is cellobiose octaacetate.
4. Use as claimed in any one of claims 1 to 3 wherein the carrier is a reducing sugar.
5. Use as claimed in claim 4 wherein the carrier is lactose.
6. Use as claimed in any one of claims 1 to 5 wherein the ternary agent is present in an amount of from 0.1 to 20% w/w based on the total weight of the composition.
7. Use as claimed in any one of claims 1 to 6 wherein the active ingredient substance is present in an amount of from 0.01% to 50% w/w based on the total weight of the composition.
8. Use as claimed in any one of claims 1 to 7 wherein the drug substance is one which includes the group $\text{Ar-CH(OH)-CH}_2\text{-NH-R}$.
9. Use according to claim 8 wherein said drug substance is selected from:
 - 3-(4-[[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy)butyl) benzenesulfonamide;
 - 3-(3-[[7-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)-amino)heptyl]oxy)propyl)benzenesulfonamide;
 - 4-((1R)-2-[(6-[2-[(2,6-dichlorobenzyl)oxy]ethoxy)hexyl]amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol and

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4-((1*R*)-2-((6-(4-[3-(cyclopentylsulfonyl)phenyl]butoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol,
or a salt, solvate or physiologically acceptable derivative thereof.

10. Use as claimed in any one of claims 1 to 9 wherein the solid pharmaceutical formulation is for administration by inhalation.

11. Use as claimed in any one of claims 1 to 10 wherein the solid pharmaceutical formulation comprises two or more active drug substances

12. An inhalable solid pharmaceutical formulation comprising

(a) an active ingredient substance susceptible to chemical interaction with lactose, said active ingredient substance selected from:

3-(4-((6-((2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl)oxy)butyl) benzenesulfonamide;

3-(3-((7-((2*R*)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl)phenyl]ethyl)-amino)heptyl)oxy)propyl)benzenesulfonamide;

4-((1*R*)-2-((6-(2-((2,6-dichlorobenzyl)oxy)ethoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol and

4-((1*R*)-2-((6-(4-[3-(cyclopentylsulfonyl)phenyl]butoxy)hexyl)amino)-1-hydroxyethyl)-2-(hydroxymethyl)phenol,

or a salt, solvate or physiologically acceptable derivative thereof,

(b) lactose and

(c) cellobiose octaacetate.

13. An inhalable solid pharmaceutical formulation as claimed in claim 12 further comprising one or more of the features described in any one or more of claims 6 to 7.

14. A method of reducing or inhibiting chemical interaction between an active ingredient substance and a carrier susceptible to chemical interaction, which comprises mixing a ternary agent which is a sugar ester with said active ingredient substance and said carrier.

15. A method of reducing or inhibiting chemical degradation of an active ingredient substance in a formulation comprising a carrier and an active ingredient substance,

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which method comprises mixing a ternary agent which is a sugar ester with said active ingredient substance and said carrier.

16. A method as claimed in claim 14 or 15 wherein the ternary agent is cellobiose octaacetate.

17. A method as claimed in claim 14 or 15 further comprising one or more of the features described in any one or more of claims 4 to 11.

18. Use of an inhalable solid pharmaceutical formulation as claimed in either of claims 12 or 13 for the manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease or rhinitis, including seasonal and allergic rhinitis.

19. A method for treating asthma, chronic obstructive pulmonary diseases (COPD), chronic or wheezy bronchitis, emphysema, respiratory tract infection, upper respiratory tract disease, or rhinitis, comprising administering to a patient in need thereof an inhalable solid pharmaceutical formulation as claimed in either of claims 12 or 13.